PATENT APPLICATION

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re application of:

Bruno CRIERE et al.

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PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE

PREPARATION METHOD

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450

Sir:

- I, George Bobotas, Ph.D., hereby declare and affirm that:
- 1. I am employed as Vice President, Scientific Affairs at Reliant Pharmaceuticals, Inc., the exclusive licensee of the above-identified patent application.
- 2. I have over 25 years of clinical and scientific affairs experience with leading pharmaceutical and clinical development organizations. I have extensive research experience and am a member of numerous professional organizations, including the American Association for the Advancement of Science, the New York Academy of Science, and the American Chemical Society. I previously worked as the Executive Director, CNS Center for Covance Inc., where I managed the operational, scientific, and financial aspects of the Center. Prior to Covance, I led Scientific Affairs and Licensing for Somerset Pharmaceuticals, Inc., New Product Licensing and Evaluation for Mylan Laboratories Inc., and

biochemistry and pharmacokinetics for Forest Laboratories, Inc. In addition, I am a listed inventor on five issued U.S. Patents and numerous U.S. patent applications. I hold a Doctorate in Biochemistry from City University of New York and Masters Degrees in Biochemistry from the City University of New York and in Physical Chemistry from Smith College.

3. I am submitting this Declaration in support of the referenced patent application. I am familiar with the subject matter described and claimed in the application. I am also familiar with U.S. Patent No. 4,895,726 ("the '726 patent") and U.S. Patent No. 6,074,670 ("the '670 patent").

Comparison Of Formulations Covered By The Present Invention To Commercial Embodiments Of The '726 Patent And The '670 Patent

4. I designed and supervised the performance of a comparison between pharmaceutical formulations covered by the present invention and commercial embodiments of the '726 and '670 patents. Several sets of comparative data are presented in this Section (Studies A, B and C). The data show that, with a healthy low-fat diet, on a per-milligram basis, fenofibrate formulations according to the present invention are more bioavailable than the commercial fenofibrate formulations covered by the '726 patent and/or the '670 patent. The data also show that by increasing the percentage of fenofibrate and reducing the percentage of polymer (in comparison to the amounts disclosed in the '670 patent), we can achieve a substantial increase in fenofibrate bioavailability, which, in turn, permits a substantial reduction in fenofibrate dosage while providing the same therapeutic effect.

Study A

5. Study Design - A randomized, single-dose, crossover study to assess the

relative bioavailability of 130 mg ANTARA® fenofibrate capsules¹ versus 200 mg TRICOR® fenofibrate capsules² in healthy adult subjects following consumption of a therapeutic lifestyle change (TLC) meal. 29 healthy adult males and females completed the study. Following randomization, subjects received a single dose of medication at the beginning of each treatment period. After completion of the first period, subjects crossed over. A washout period of at least 14 days occurred between treatment periods. Blood samples for the determination of plasma fenofibric acid were drawn prior to dosing and periodically up to 168 hours after dosing.

6. Pharmacokinetic Results – The following TABLE 1 summarizes selected pharmacokinetic parameters for fenofibric acid following a TLC meal (arithmetic mean (± SD)) and the ratios of least square means for 1n-transformed data (with 90% confidence intervals):

TABLE 1

Parameter	Treatment A: 130 mg ANTARA® capsules	Treatment B: 200 mg TRICOR® capsules	Ratio of LSM A/B% (90% CI)
AUC _{0-∞} (ng·h/ml)	132,387 (±40,251)	162,332 (±45,509)	83.2 (75.9-91.3)
C _{max} (ng/ml)	7,565 (±1,593)	7,554 (±2,934)	105.7 (90.5-123.5)
T _{max} (h)	4.21 (±0.632)	4.58 (±0.508)	N/A

7. The following TABLE 2 compares the relative bioavailability of the 130 mg fenofibrate formulation covered by the present invention, versus the 200 mg TRICOR® capsules covered by the '726 patent, on a per-milligram basis by

¹ This product, distributed by Reliant Pharmaceuticals, Inc., is covered by the present invention. The exact formulation of ANTARA® is a trade secret.

² Abbott Laboratories, Inc., the distributor of 200 mg TRICOR® fenofibrate capsules, listed the '726 patent in the Food and Drug Administration's "Approved Drug Products With Therapeutic Equivalence Evaluations" (also known as the "Orange Book") as covering the product.

Declaration under 37 C.F.R. § 1.132 U.S. Application No. 10/030,262

comparing $AUC_{0-\omega}$

TABLE 2

Treatment	Mean AUC₀.∞	Mean AUC _{0-∞} per mg fenofibrate	% increase in bioavailability per mg
130 mg ANTARA® capsules	132,387	1,018	25.5%
200 mg TRICOR® capsules	162,332	811	

8. Conclusions – This single dose study compared the bioavailability of 130 mg ANTARA® fenofibrate capsules covered by the present invention, versus 200 mg TRICOR® fenofibrate capsules covered by the '726 patent, in subjects following consumption of a TLC meal. The formulation according to the present invention (130 mg ANTARA® capsules) showed a 25.5% increase in bioavailability on a per-milligram basis, as compared to the formulation covered by the '726 patent (200 mg TRICOR® capsules).

Study B

9. Study Design – A randomized, multiple-dose, crossover study to assess the relative bioavailability of 130 mg ANTARA® fenofibrate capsules versus 200 mg TRICOR® fenofibrate capsules at steady state in healthy adult subjects on a therapeutic lifestyle change (TLC) diet. 26 healthy adult males and females completed the study. Following randomization, subjects received a single dose of medication daily for 7 days. After completion of the first period, subjects crossed over to the alternate treatment for 7 days. A washout period of at least 14 days occurred between treatment periods. Blood samples for the determination of plasma fenofibric acid were drawn on day 1 prior to the first dosing and at steady state on day 7 of each treatment period, just prior to

administration of the final dose of the study drug (time 0) and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours postdose. Trough blood samples were taken on days 4, 5, 6, 7 and 8 of each treatment period to establish whether steady state had been reached.

10. Pharmacokinetic Results – The following TABLE 3 summarizes selected pharmacokinetic parameters for fenofibric acid at steady state following a TLC meal (arithmetic mean (± SD)) and the ratios of least square means for 1n-transformed data (with 90% confidence intervals):

TABLE 3

Parameter	Treatment A: 130 mg ANTARA® capsules	Treatment B: 200 mg TRICOR® capsules	Ratio of LSM A/B% (90% CI)
AUC _{τ, ss} (ng·h/ml)	182,889 (±53,669)	204,988 (±50,945)	88.4 (84.0-93.0)
C _{max, ss} (ng/ml)	12,664 (±2,685)	13,810 (±2,781)	91.7 (85.1-98.7)
T _{max, ss} (h)	4.89 (±0.978)	5.34 (±1.281)	N/A

11. The following TABLE 4 compares the relative bioavailability of the 130 mg fenofibrate formulation covered by the present invention, versus the 200 mg TRICOR® capsules covered by the '726 patent, on a per-milligram basis by comparing AUC_{7, ss}:

TABLE 4

Treatment	Mean AUC _{τ, ss}	Mean AUC $_{\tau, ss}$ per mg fenofibrate	% increase in bioavailability per mg
130 mg ANTARA [®] capsules	182,889	1,406	37.3%

200 mg	204,988	1,024	
TRICOR®			·
capsules			

12. Conclusions – This multiple-dose study compared the bioavailability of 130 mg ANTARA® fenofibrate capsules covered by the present invention, versus 200 mg TRICOR® fenofibrate capsules covered by the '726 patent, at steady state in subjects on a TLC diet. The formulation according to the present invention (130 mg ANTARA® capsules) showed a 37.3% increase in bioavailability on a permilligram basis, as compared to the formulation covered by the '726 patent (200 mg TRICOR® capsules).

Study C

- 13. Study Design A randomized, single-dose, crossover study to assess the relative bioavailability of 120 mg and 144 mg fenofibrate capsules covered by the present invention, versus 160 mg TRICOR® fenofibrate tablets³ in healthy adult subjects following consumption of a National Cholesterol Education Program (NCEP) Step 1 low-fat diet. 15 healthy adult males completed the study. Following randomization, subjects received a single dose of medication at the beginning of each treatment period. After completion of each period, subjects crossed over. A washout period of at least 7 days occurred between treatment periods. Blood samples for the determination of plasma fenofibric acid were drawn prior to dosing and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours after dosing.
- 14. Pharmacokinetic Results The following TABLE 5 summarizes selected pharmacokinetic parameters for fenofibric acid following a NCEP Step 1 low-fat

³ Abbott Laboratories, Inc., the distributor of 160 mg TRICOR® fenofibrate tablets, listed the '670 patent in the FDA's Orange Book as covering the product. (The '726 patent is also listed; however, the '726 patent claims only cover capsules, not tablets, and therefore the '726 patent is not relevant to this product.)

Declaration under 37 C.F.R. § 1.132 U.S. Application No. 10/030,262

diet (arithmetic mean (± SD)) and the ratios of least square means for 1n-transformed data (with 90% confidence intervals):

TABLE 5

Parameter	Treatment A: 120 mg fenofibrate capsules	Treatment B: 144 mg fenofibrate capsules	Treatment C: 160 mg TRICOR® tablets	Ratio of LSM A/C% (90% CI)	Ratio of LSM B/C% (90% CI)
AUC _{0-∞} (ng·h/ml)	115,452 (±18,889)	132,467 (±22,929)	128,305 (±30,672)	91.6 (86.8-96.7)	105.1 (99.6- 110.8)
C _{max} (ng/ml)	7,669 (±1,234)	8,750 (±1387)	6,708 (±1,488)	115.1 (104.1- 127.2)	131.3 (118.8- 145.1)
T _{max} (h)	4.07 (±0.863)	4.30 (±0.702)	3.93 (±0.728)	N/A	N/A

15. The following TABLE 6 compares the relative bioavailability of the 120 mg and 144 mg fenofibrate formulations covered by the present invention, versus the 160 mg TRICOR[®] tablets covered by the '670 patent, on a per-milligram basis by comparing AUC_{0-∞}:

TABLE 6

Treatment	Mean AUC₀-∞	Mean AUC _{0-∞} per mg fenofibrate	% increase in bioavailability per mg
120 mg fenofibrate capsules	115,452	962	20.0%
144 mg fenofibrate capsules	132,467	920	14.7%
160 mg TRICOR [®] tablets	128,305	802	

16. Conclusions – This single dose study compared the bioavailability of 120 mg and 144 mg fenofibrate capsules covered by the present invention, versus 160 mg TRICOR® fenofibrate tablets covered by the '670 patent, in subjects following consumption of a NCEP Step 1 low-fat diet. The formulations according to the present invention (120 mg and 144 mg capsules) showed a 20.0% and 14.7% increase, respectively, in bioavailability on a per-milligram basis, as compared to the formulation covered by the '670 patent (160 mg TRICOR® tablets).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent(s) issuing therefrom.

Date:

George Bobotas

List of Attachments

- A. Product Insert Lipidil®
- B. Product insert Tricor® (67, 134 & 200 mg)
- C. 2002 Orange Book listing for Tricor®
- D. Product insert Tricor® (54 mg and 160 mg)
- E. Product insert for Tricor® (48 & 145 mg)
- F. Product insert for Antara®

LIPIDIL®
(Fenofibrate Capsules)

DESCRIPTION

LIPIDIL (fenofibrate capsules of a lipid regulating agent. It is available as capsules for oral administration. Each capsule contains 100 mg of fenofibrate. Each capsule also contains lactose, NF magnesium stearate, NF, and pregelatinized starch, NF. The chemical name is 2-(4-(4-chlorobenzoy) phenoxy)-2-methylpropanoic and 1 methylethyl ester with the following structural formula:

CLINICAL PHARMACOUCH 1

The effects of LIPIDIL 100 mg nd on serum triglycerides were studied in two randomized, double-blind clinical trials¹. 147 hypertriglyceridemic patients (Types IV and V) were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TC levels of 250 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with 0: without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with LIPIDIL decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol as seen in the following table of changes seen at the end of treatment in patients with triglycerides of 500 to 1500 mg/dL.

Changes in Lipid and Lipoprotein Determinations. Type IV/V Patients

	Ĩ, āc	i, acepo		LIPIDIL (100 mg tid)	
- 	Basen (f 'Aea '7 f	% Change	Baseline Mean (mg/dL)	% Change	Net Difference (of %)
Triglycerides Total VLDL	· ,	+ 7 + 19	726 543	- 55 31	- 62 - 70
Cholesterol Total HDL LDL VLDL	2.° 101 201	0 + 5 - 4 + 11	261 30 1 03 1 26	14 - 23 + 45 - 49	- 14 + 18 + 49 - 60

The mechanism of action of LIPIDIL has not been clearly established in man. Fenofibric acid, the active metabolite of fenofibrate, lowers plasma triglycerides apparently by inhibiting triglyceride synthesis, resulting in a reduction of VLDL released into the circulation, and also by stimulating the catabolism of triglyceride-rich lipoprotein i.e., VLDL). LIPIDIL also reduces serum uric acid levels in hyperunicemic and normal individuals by increasing the uninary excretion of uric acid.

Fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% or a single radiolabelled 300 mg dose of fenofibrate appeared in the unner primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration, and the compound is eliminated with a half-life of 20 nours. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with 100 mg/day, and did not demonstrate accumulation across time following multiple dose administration. In elderly volunteers 77-87 years of age, the oral clearance of fenofibric acid following a single oral dose of 100 mg was 1.2 L/h, which compares with 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

In a study in patients with severe renal impairment (creatinine clearance < 50 ml/min), the rate of clearance of fenofibric acic was greatly reduced, and the compound accumulated during chronic dosage

However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 ml/min) the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults. Therefore, the dosage of LIPIDIL should be reduced in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

INDICATIONS AND USAGE

LIPIDIL (fenofibrate capsules) is indicated as adjunctive therapy to diet for treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who are at risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dL and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycarides below 1000 mg/dL are unlikely to present a risk of pancreatitis. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronomia thereby obviating the need for pharmacologic intervention. LIPIDIL therapy may be considered for these subjects with triglyouride elevations between 1000 and 2000 mg/dL who have a history of pancrealitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronomia, but the influence of LIPIDIL therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hypeslipeproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia2.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiszide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because the benefit/risk ratio of LIPIDIL (fenofibrate) has not been established in clinical trials of primary or secondary prevention to reduce the risk of developing coronary heart disease, LIPIDIL is not indicated for such use. (See WARNINGS and PRECAUTIONS).

CONTRAINDICATIONS

- 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.
- 2. Preexisting gallbladder disease (see WARNINGS).
- 3. Hypersensitivity to fenofibrate.

WARNINGS

1. Because of chemical, pharmasological, and clinical similarities between LIPIDIL (ferofibeate), Atromid-S (clofibrate), and Lapid (genefibrate)), the adverse findings in 4 large randomized, placebo-controlled elizated studies with these other fibrate drugs may also apply to LIPIDIL. In the first of these studies, the Coronary Drug Project, 1000 subjects with previous myocandial infarction were treated for 5 years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 2000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed chelcithiasis and cholocystitis requiring surgery. In a study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for 5 years and followed 1 year beyond. There was a statistically significant, 44% higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystactomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for galibladder disease was confirmed.

During the 5 year primary prevention component of the Helsinki Heart Study involving 4081 middle-aged males treated with either gamiltonil or placebo, and the 3.5 year open extension, total mortality was 22% higher in the original gamiltonil randomization group (p=0.19, 95% confidence interval for relative risk G:P=0.91-1.64). Cancer deaths trended higher in the gamiltonil group (p=0.11), while cancers (excluding basal cell carcinoma) were diagnosed in 2.5% of patients in both treatment groups. Because of the more limited size of the Helsinki

Heart Study, the relative risk of death from any cause did not differ statistically from the relative risk of 1.29 clofibrate/placebo observed at the 9 year follow-up of the WHO study. Similarly, the numerical excess of guilbladder surgeries in the gumfibrozil group (0.9% vs. 0.5% with placebo) did not differ statistically from the excess observed in the clofibrate group compared to placebo in the WHO study.

The secondary prevention component of the Helsinki Heart Study involved 628 middle-aged males excluded from the primary prevention study because of known or suspected coronary heart disease and treated with either gemfibrozil or placebo for 5 years. Cardiac deaths trended higher in the gemfibrozil group (17/311 vs. 8/317 placebo patients, p=0.06, hazard ratio 2.2, 95% confidence interval for hazard ratio = 0.94-5.05). Galibladder surgery was more frequent in the gemfibrozil group (1.9% vs. 0.3%, p=0.07), as was appendectomy (6 cases on gemfibrozil vs. 0 on placebo, p=0.029).

Liver Function: Femolihente use at doses of 200 to 300 mg/day is associated with significant increases in serum transmissess [AST-(SGOT) or ALT (SPGT)]. Increases to > 3 times the upper limit of normal command in 6.3% of LIPIDIL-treated patients taking 200 to 300 mg/day in controlled multiple-dose trials lasting 8-24 weeks.

Patients with AST or ALT > 3x the Upper Normal Limits in Controlled Clinical Trials vs Penofibrate (200 to 300 mg/day)

	N	# Events	Events Rate
Control	336	4	1.2%
Fenofibrate	442	28	6.3%

When transaminase determinations were followed either after discontinuation of treatment or during continued transaminase determinations remained above normal limits was usually observed. However, the transaminase determinations remained above normal limits in 2 of the 28 patients (7.1%) at the end of follow-up off transment. Fenofibrate hepatotoxicity appears to be dose-related. In an 8-week dose-ranging study the incidence of ALT or AST elevations at least three times the upper limit of normal was 13% in patients receiving 200 or 300 mg/day and was 0% in those receiving 100 or 50 mg/day, or placebo. Both hepatocellular and cholestatic hepatitis have been reported. In literature reports, hepatitis associated with fenofibrate has occurred after exposures of weeks to several years.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed

for the duration of therapy with LIPIDIL, and therapy discontinued if enzyme levels persist above three times the normal limit.

- 3. Cholelithiasis. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the gemfibrozil -treatment group. Fenofibrate, like clofibrate and gemfibrosil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. LIPIDIL therapy should be discontinued if gallstones are found.
- 4. Concomitant Oral Anticoagulants. Caution should be exercised when anticoagulants are given in conjunction with LIFIDIL because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.
- 5. Concomitant therapy with LIPIDIL and HMG-CoA reductors inhibitors (such as lovastatin, preventatin, and simulatin). No data exists on this combined therapy. The association of the chemically and phesoscologically related similar compound genefibrozil and Mevacor® (lovastatin) has been associated with shabdomyulyala, manhadly elevated creatine kinese (CK) levels and myoglobinesia, leading in a high proportion of cases to acute renal failure.

In virtually all patients who have had an unsatiofactory lipid response to either drug alone, any potential lipid benealt of combined thompy with HMG CoA reductace inhibitous and LIPIDIL does not outweigh the risks of severe myspethy, shabdomyslysis, and acute remainishers. The use of fibrates alone, including LIPIDIL, may occasionally be associated with myositis, myopathy, or shabdomyolysis. Patients receiving LIPIDIL and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, LIPIDIL therapy should be stopped.

6. The effect of LIPIDIL on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. LIPIDIL should be administered only to those patients in described under INDICATIONS AND USAGE. If a significant reduction in fasting chylomicronemia does not occur, LIPIDIL should be discontinued.

Revised: November 12, 1993

PRECAUTIONS

- Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting LIPIDIL therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.
- Continued therapy: Periodic determination of serum lipids should be obtained during initial
 therapy in order to establish the lowest effective dose of LIPIDIL. Therapy should be withdrawn
 in patients who do not have an adequate response after two months of treatment with the
 maximum recommended dose of 300 mg/day.
- 3. Pancreatitis has been seperted in patients taking feneliheats, gamiliocali, and ciofficate. This occurrence may represent a failure of efficacy or a secondary phenomenon through biliary tract stone or sludge formation and obstruction of the common bile duct.
- 4. Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with LIPEDEL. Unicaria was seen in 1.25 vs 0%, and rash in 2.82 vs 1.23% of fenofibrate and placebo patients respectively in controlled trials.
- 5. Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of LIPIDIL therapy. However, these levels stabilize during long-turm administration. Extremely rare spontaneous reports of thrombocytopenia and aganuslocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of LIPIDIL administration.
- 6. Skeletal numerie: The use of fibrates alone, including LIPIDIL may occasionally be associated with myositis. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse mysigias, muscle tenderness or weakness, and/or marked elevations of creatinine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

7. Drug interactions:

- (A) Oral Anticongmission: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LIPIDIL. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHEROMENT TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. PROQUENT PROTHEROMEN DEFENDED ARE ADVISABLE UNTIL IT HAS BEEN DEPORTELY DETERMINED THAT THE PROTHEROMEN LEVEL HAS STABILIZED.
- (B) HhdG-CoA seductors inhibitors: Rhebdenyolysis has occurred when lovariatin was administered in continued through with genfibrent, a compound of the fibrate class soluted to fenciliosis. In most pathents who have had an unsatisfactory lipid response to either deng alove, any possible bandle of constitued through with an HMG-CoA reductors inhibitor and LIPIDIL is not outweighted by the sists of severe myopathy, rhebdenyolysis, and acute renal fathers. There is no assurance that periodic mostlessing of creating kinase will prevent the occurrence of severe myopathy and hidney damage.
- (C) Resine: Since bile acid sequestrants may bind other drugs given concurrently, patients should take LIPIDEL at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.
- (D) Cyclespesia: Because cyclesporin can produce nephrotoxicity with decrease in creatine clearance and rises in serian creatinine, and because renal excretion is the primary elimination route of fibrate drugs including LIPIDIL, there is a risk that an interaction will lead to deterioration. The benefits and risks of using LIPIDIL with immunosuppressants and other potentially rephrotoxic agents should be carefully considered, and the lowest effective dose 'employed.
- 8. Carrinogenesis, Mutagenesis, Impairment of Pertility: In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter³ of sunface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum.

Revised: November 12, 1998

recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter³ surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gamfibroxil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter³ surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibroxil while testicular integritidal cell tumess were increased in males on all three drugs.

In a 21-month study in mise at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/mster² surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both make and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled. DNA synthesis.

9. Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter² surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gustation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifids.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, viscoral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through wearing caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

- 10. Number mothers: For eithers should not be used in number mothers. Because of the potential for tumoriganicity seen in animal studies, a decision should be made whether to discontinue running or to discontinue the drug.
- 11. Use in Children: Safety and efficacy in children have not been established.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 1% or more of patients treated with LIPIDIL during the six month and the eight week double-blind, placebo-controlled trials in the U.S.¹⁹ are listed in the table below. Adverse events led to discontinuation of treatment in 6% of patients treated with LIPIDIL and in 2% treated with placebo. Skin rashes were the most frequent events, causing discontinuation of LIPIDIL treatment in 2% of patients in double-blind trials.

Page 11

DDY SYSTEM	LIPIDEL	PLACEBO
Advance Event	(N = 191)	(N = 183)
ODY AS A WHOLE		
Agthenia/Fatigue	5%	3%
Infections	18%	15%
Flu Syndrome	5%	2%
Localized/Misc. Pain	8%	7%
Headache	5%	4%
ARDIOVASCULAR	•	
	1%	2%
Arrhythmia		
OIGESTIVE	5%	7%
Dyupopoio Torrestor	1%	0%
Eructation	3%	2%
Flatulence	4%	3%
Neuman/Vomiting	35	3%
Abdominal Pain	35	2%
Countination	3% 3%	. 7%
Dissilon		3
MUSCULOSSELETAL		4%
Arthrolgin	3%	**
NERVOUS		1%
Descused Libido	2%	25
Perusthenia ·	. 15	1%
Incurred Appetite	1%	1%
Diminus	25	15
Esperanta	., 15	179
RESPERATORY		
Cough	1%	1%
Rhistitis	4%	3%
Simusitie	1%	15
skin & aftendages		
Progitos	3%	1%
. Rash	6%	2%
SPECIAL SENSES		
Emache	1%	1%
Eye Planters	1%	0%
Bluered Vision	1%	1%
Conjunctivitis	15	2%
Bye Initiation	2%	1%
UROGENITAL.		
Polyuria	1%	1%
Vaginitis	. 15	. 1%

Additional clinical adverse events reported by fewer than 1% of patients in the U.S. double-blind studies, those reported in other clinical trials, and spontaneously reported in post-marketing surveillance outside the U.S. are listed below, categorized by causality:

PROBABLY CAUSALLY RELATED: Digestive: hepatitis, cholelithiasis, cholecystitis, hepatomegaly; Musculuslaslasis: myalgia, myasthenia, rhabdomyolysis; Skin and appendages: photosensitivity, eczema; Respiratory: allergic pulmonary alveolitis.

CAUSAL RELATIONSHIP NOT ESTABLISHED: Body as a whole: facial edema, weight decrease, fever, epistesis; Cardiovascular: peripheral edema, angina, palpitations, tachycardia, migraine; Dignetive: hematemeels, penessentitis; Respiratory: congestion; Nervous: dry mouth, vertigo, anxiety, sleep disorders, confusion; Stein and appendages: lupus-like syndrome, ichthyosis, telangioctasis, alopecia; Special senses: amblyopia, tirmitus; Urogenital: decreased male fertility, renal lithlasis.

LABORATORY: In the two U.S. placebo controlled studies, serum transminase determinations (SGPT and/or SGOT) were increased to over three times the upper normal limit in 8 to 10% of patients taking Lipidil at deese of 300 mg/day (See WARNINGS). Other changes that occurred more frequently during Lipidil treatment compared to placebo included increases in creatinine and blood urea, and decreases in homoglobin and usic acid.

Additional laboratory findings that have been reported during fenofibrate treatment that are probably causally related include: anemia, leucopenia, eosinophilia, thrombocytopenia, and increased creatinine phospholimase.

DOSAGE AND ADMENISTRATION

Patients should be placed on an appropriate triglyceride-lowering diet before receiving LIPIDIL, and should continue this diet during treatment with LIPIDIL.

LIPIDIL should be given with meals. The initial dose is usually 100 mg per day, depending on the physician's assessment of the patient's risk for pancrestitis (see INDICATIONS AND USAGE). Dosage should be individualized according to patient response, and should be increased sequentially if necessary following repeat serum triglyceride estimations at 4-to-8 week intervals. The maximum dose is 300 mg/day.

<u>:</u>

Treatment with LIPIDIL should be initiated at a dose of 100 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and triglyceride levels at this dose. In the elderly, the initial dose should likewise be limited to 100 mg/day.

OVERDOSAGE

Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

LIPIDIL (funofibrate) is available as apaque white hard gulatin capsules. Each capsule contains 160 mg fenofibrate. Each capsule is pointed with "LIPIDIL". LIPIDIL is available in bottles of 90 and bottles of 1000.

NDC 9987-6799-43 NDC 9987-0799-43 Bottles of 90 Bottles of 1000

STORAGE

Store in a cool dry place. Protect from temperatures above 30°C (86°F). Avoid excessive light and humidity.

Distributed by

FOURNIER RESEARCH INC.
689 Mamaroneck Avenue
P.O.Box 340
MAMARONECK
N.Y. 10543

CAUTION-Federal law prohibits dispensing without prescription.

REFERENCES

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-304/S005

FINAL PRINTED LABELING

TRICOR ®

(fenofibrate capsules), micronized

R_x Only

DESCRIPTION

TRICOR (fenofibrate capsules), micronized, is a lipid regulating agent available as capsules for oral administration. Each capsule contains 67 mg, 134 mg or 200 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid. 1-methylethyl ester with the following structural formula:

The empirical formula is $C_{20}H_{21}O_4C1$ and the molecular weight is 360.83: fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each capsule also contains crospovidone, iron oxide, lactose, magnesium stearate, pregelatinized starch, sodium jauryl sulfate, and titanium dioxide.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo Al and apo All) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAl and apoAlI.

The effects of fenofibric acid seen in clinical practice have been explained in vivo in transgenic mice and in vitro in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPAR α). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein α -III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for

cholesterol receptors and are catabolized rapidly. Activation of PPARa also induces an increase in the synthesis of apoproteins A-l, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Clinical experience has been obtained with two different formulations of fenofibrate: a "micronized" and "non-micronized" formulation, which have been demonstrated to be bioequivalent. Comparisons of blood levels following oral administration of both formulations in healthy volunteers demonstrate that a single capsule containing 67 mg of the "micronized" formulation is bioequivalent to 100 mg of the "non-micronized" formulation. Three capsules containing 67 mg TRICOR are bioequivalent to a single 200 mg TRICOR capsule... Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of -fenofibric acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With micronized fenofibrate, the absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with single oral doses equivalent to 67 mg TRICOR and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. - -Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid-undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily tenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate. approximately 60% of the dose appeared in the uring and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenoistric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

Page 3 of 13 CR 20-01404 DN0530V4 April 11, 2000

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate. Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency. Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 200 mg TRICOR per day were assessed from-four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL: and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

ent Change in Lipid Parameters at End of Treatment

Treatment Group	Total-C	LDL-C	HDL-C	TC
Pooled Cohort Mean baseline lipid values (n=646) All FEN (n=361) Placebo (n=285)	306.9 mg/dL -18.7%* -0.4%	213.8 mg/dL -20.6%*	52.3 mg/dL +11.0%*	191.0 mg/dl -28.9%*
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)	-0.4%	-2.2%	+0.7%	+7.7%
Mean baseline lipid values (n=334) All FEN (n=193) Placebo (n=141)	307.7 mg/dl_ -22.4%* +0.2%	227.7 mg/dL -31.4%* -2.2%	58.1 mg/dL +9.8%*	101.7 mg/dl -23.5%*
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)		2.276	+2.6%	+11.7%
Mean baseline lipid values (n=242) All FEN (n=126) Placebo (n=116)	312.8 mg/dL -16.8%* -3.0%:	219.8 mg/dL -20.1%* -6.6%	46.7-mg/dl. +14.6%* +2.3%	231.9 mg/dL -35.9%* +0.9%

Duration of study treatment was 3 to 6 months.

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind. placebo-controlled clinical trials of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 200 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

p = <0.05 vs. Placebo

Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	Plac	ebo				COR	upreviuse	
Baseline TG levels 350 to 499 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	28	449	450	-0.5	27	432	223	-46.2°
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	. 34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	
VLDL Cholesterol	27	99	99	5.8	27	92	46	14.5
Study 2	Plac	ebo				COR	40	-44.7*
Baseline TG levels 500 to 1500 mg/dL	N.	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	44	710	750 _	_ 7.2	48	726	308	-54.5*
								- 144 1-
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
VLDL Triglycerides Total Cholesterol	29 44	537 272	571 271			543	205	-50.6*
Total Cholesterol HDL Cholesterol				18.7 0.4 5.0	33 48 48		205 223	-50.6* -13.8*
7	44	272	271	0.4	48	543 261	205	-50.6*

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet for the reduction of LDL-C. Total-C. Triglycerides and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2.000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I: IV and V hyperlipoproteinemia.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as

hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

• _		Lipid Elevation	
Туре	Lipoprotein Elevated	·Major	Minor
l (rare)	chylomicrons	TG	- 1-C
lla	LDL	- C	
llb	LDLVLDL	·- č	TG
III (rare)	IDL	C, TG	
IV	VLDL	TG	1-C
V (rare)	chylomicrons, VLDL	TG	1-

(=choiesterol.

TG=trigly cerides

LDI =low density lipoprotein

VLDI =very iow density lipoprotein

IDI =imermediate density lipoprotein

The NCEP Treatment Cuideline

_		Autorices Arenthent Officelities		•
	Definite Athlerosclerotic Disease*	Two or More Other Risk Factors ^b	LDL-Cholesteral mg/dL (mmol/L)	
_		•	Initiation Level	Goal
	No	No	≥ 190 (≥ 4.9)-	< 160 (< 4.1)
-	- No	Yes	2 160 (2 4.1)	< 130 (< 3.4)
121	Yes	Yes or No	≥ 130° (≥ 3.4)	< 100 (< 2.6)

oronary heart disease or peripheral vascular disease tincluding symptomatic carotid artery disease).

(b) Other risk factors for coronary heart disease (CHD) include age (males. 245 years; females: 255 years or premature menopause without estrogen replacement therapy); family history of premature CHD, current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol 1.), and disheres mellitus Subtract 1 risk factor if HDL-C is >60 mg/dL (>1.6 mmol/L)

(* In CHD patients with EDL-C levels 100 to 129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS:

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 134 mg to 200 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose-related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper

limit of normal was 13% in patients receiving dosages equivalent to 134 mg to 200 mg TRICOR per day and was 0% in those receiving dosages equivalent to 34 mg or 67 mg TRICOR per day. or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of TRICOR and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tendemess, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and noncardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate capsules), micronized. Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy,

post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group.(6/311 vs. 0/317, p=0.029).

PRECAUTIONS.

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 200 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson Syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration:

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg: 0.3. 1, and 6 times the maximum recommended human dose on the basis of mg/meter² of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter² surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) 'multiples based on mg/meter' surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter² surface area). there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter² surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS _

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events. causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE	(1. 607)	(N-363)
Abdominal Pain	4.6%	4.4% -
Back Pain	3.4%	2:5%
Headache	3.2%	2.7%
Asthenia —	2.1%	3.0%
-Flu Syndrome DIGESTIVE	2.1%-	- 2.7%
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	1.1%
Nausea .	2.3%	1.9%
Constipation METABOLIC AND NUTRITIONAL DISOR	2.1%	1.4%
CONTINUE AND NOTRITIONAL DISOR	CDERS .	
SGPT Increased - Creatine Phosphokinase Increased	 3.0%	. 1.6%
SGOT increased	3.0%	1.4%
RESPIRATORY	3.4% **	0.5%
Respiratory Disorder	£ 34.	
Rhinitis	6.2% -	5.5%
Dosage equivalent to 200 mg TRICOR	2.3%	. 1.1%

^{**} Significantly different from Piacebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation. DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, nausea, vomiting, and diarrhea.

ENDOCRINE SYSTEM: Diabetes mellitus

HEMIC AND LYMPHATIC SYSTEM: Anemia. leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain. hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema. MUSCULOSKELETAL SYSTEM: Myositis..myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, parasthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.

SKIN AND APPENDAGES: Rash, pruritis, eczema, herpes zoster, urticaria, acne. sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynocomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage: usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR should be given with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 200 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 67 to 200 mg per day. Dosage _ should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 200 mg per day.

Treatment with TRICOR should be initiated at a dose of 67 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 67 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR® (fenofibrate capsules), micronized, is available as hard gelatin capsules in three strengths:

67 mg yellow capsules, imprinted with Ξ on cap and Abbo-Code identification letters FR on body, available in bottles of 90 (NDC 0074-4342-90) and Abbo-Pac packages of 100 (NDC 0074-4342-11).

134 mg white capsules, imprinted with Ξ on cap and Abbo-Code identification letters AR on body, available in bottles of 90 (NDC 0074-6447-90) and Abbo-Pac packages of 100 (NDC 0074-6447-11).

200 mg orange capsules, imprinted with \(\mathbb{B}\) on cap and Abbo-Code identification letters SR on body, available in bottles of 90 (NDC 0074-6415-90) and Abbo-Pac packages of 100

(NDC 0074-6415-11).

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Laboratoires Fournier, S.A., 21300 Chenôve, France

Made in France

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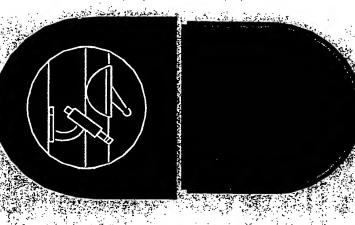
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ABBOTT



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APPROVED

HILLY

THERAPEUTIC EQUIVALENCE EVALUATIONS

22nd EDITION

THE PRODUCTS IN THIS DIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
EGOD AND BRUG ADMINISTRATION
CENTERIEDR DRUGIEVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATAMANAGEMENT AND SERVICES

PRESCRIPTION DRUG PRODUCT LIST

ABBOTT	TABLET; ORAL	4	-		TRICOR (MICRONIZED)			SEE ENALAPRIL MALEATE;		+		ASTRAZENECA	TABLET, EXTENDED RELEASE;	FELODIPINE		+	WALLACE LABS	TABLET; ORAL	SUSPENSION; ORAL FELBATOL LABS	FELBAMATE
54MG 160MG			200MG	134MG	67MG			FELODIPINE		IOMG	5MG	2.5MG	SE; ORAL			600MG	400MG		600MG/5ML	
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AB + DISTA	AB · WATSON LABS	AB PUREPAC PHARM	AB PAR PHARM	AB MYLAN	AB MUTUAL PHARM	AB LEDERLE	AB IVAX PHARMS	AB GENEVA PHARMS	FENOPROFEN CALCIUM DANBURY PHARMA	AB DISTA	NALFON 200		AB	AB PAR PHARM	AB	AB GENEVA PHARMS	CAPSULE; ORAL	FENOPROFEN CALCIUM	INJECTABLE; INJECTION CORLOPAM + ABBOTT	FENOLDOPAM MESYLATE
EQ 600MG BASE	EQ 600MG BASE	BQ 600MG BASE	EQ 600MG BASE	EQ 600MG BASE	EQ 600MG BASE	EQ 600MG BASE	EQ 600MG BASE	BQ 600MG BASE	EQ 600MG BASE	BQ 200mg break	TO COMP BACE	EO 300MG BASE	EQ 300MG BASE	BQ 200MG BASE	EQ 300MG BASE	BQ 200MG BASE			EQ 10MG BASE/ML	
N17710 001	N72407 001 AUG 17, 1988	MAY 02, 1988	AUG 17, 1988	AUG 17, 1988	N72902 001 DEC 21, 1990	N72326 001 AUG 17, 1988	N72557 001 AUG 29, 1988	N72396 001 OCT 17, 1988	N72602 001 OCT 11, 1988		N17604 003	N17604 002	N72438 001 AUG 22, 1988	N72437 001 AUG 22, 1988	N72395 001 OCT 17, 1988	N72394 001 OCT 17, 1988			N19922 001 SEP 23, 1997	

PRESCRIPTION AND OTC DRUG PRODUCT PATENT AND EXCLUSIVITY DATA

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TRICOR®

(fenofibrate tablets)

R_x Only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 54 mg or 160 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:

The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, and xanthan gum.

In addition, individual tablets contain:

54 mg tablets: D&C Yellow No. 10, FD&C Yellow No. 6, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo Al and apo All) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPAR α). Through this mechanism, fenofibrate increases lipolysis and elimination of

triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR α also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of 54 mg and 160 mg tablets are equivalent under fed conditions to 67 and 200 mg capsules, respectively.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With fenofibrate tablets, the extent of absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. *Metabolism*

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77. - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or

metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 160 mg TRICOR per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1
Mean Percent Change in Lipid Parameters at End of Treatment[†]

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8	52.3 mg/dL	191.0
All FEN (n=361)	-18.7%*	mg/dL	+11.0%*	mg/dL
Placebo (n=285)	-0.4%	-20.6%*	+0.7%	-28.9%*
		-2.2%		+7.7%
Baseline LDL-C > 160 mg/dL and				
TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7	58.1 mg/dL	101.7
All FEN (n=193)	-22.4%*	mg/dL	+9.8%*	mg/dL
Placebo (n=141)	+0.2%	-31.4%*	+2.6%	-23.5%*
		-2.2%		+11.7%
Baseline LDL-C > 160 mg/dL and				
TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8	46.7 mg/dL	231.9
All FEN (n=126)	-16.8%*	mg/dL	+14.6%*	mg/dL
Placebo (n=116)	-3.0%	-20.1%*	+2.3%	-35.9%*
		-6.6%		+0.9%

[†] Duration of study treatment was 3 to 6 months.

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 160 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

^{*} p = <0.05 vs. Placebo

Table 2
Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Pla	cebo			TR	ICOR	71 .	
N	Baselin	Endpoin	%	N	Baselin	Endpoin	%
	e	t (Mean)	Change	1	e	t (Mean)	Change
	(Mean)		(Mean)		(Mean)		(Mean)
28	449	450	-0.5	27	432	223	-46.2*
19	367	350	2.7	19	350	178	-44.1*
28	255	261	2.8	27	252	227	-9.1*
28	35	36	. 4	27	34	40	19.6*
28	120	129	12	27	128	137	14.5
27	99	99	5.8	27	92	46	-44.7*
Pla	cebo			TR	ICOR		
N	Baselin	Endpoin	%	N	Baselin	Endpoin	%
	e	t (Mean)	Change	l	e	t (Mean)	Change
	(Mean)		(Mean)		(Mean)		(Mean)
44	710	750	7.2	48	726	308	-54.5*
29	537	571	18.7	33	543	205	-50.6*
44	272	271	0.4	48	261	223	-13.8*
44	27	28	5.0	48	30	36	22.9*
42	100	90	-4.2	45	103		45.0*
42	137	142	11.0	45	126	54	-49.4*
	28 19 28 28 27 Pla N 44 29 44 44 42	e (Mean) 28 449 19 367 28 255 28 35 28 120 27 99 Placebo N Baselin e (Mean) 44 710 29 537 44 272 44 27 42 100	N Baselin e (Mean) Endpoin t (Mean) 28 449 450 19 367 350 28 255 261 28 35 36 28 120 129 27 99 99 Placebo N Baselin e (Mean) Endpoin t (Mean) (Mean) 44 710 750 29 537 571 44 272 271 44 27 28 42 100 90	N Baselin e (Mean) Endpoin t (Mean) % Change (Mean) 28 449 450 -0.5 19 367 350 2.7 28 255 261 2.8 28 35 36 4 28 120 129 12 27 99 99 5.8 Placebo N Baselin e (Mean) Endpoin t (Mean) % Change (Mean) 44 710 750 7.2 29 537 571 18.7 44 272 271 0.4 44 27 28 5.0 42 100 90 -4.2	N Baselin e (Mean) Endpoin t (Mean) % (Mean) N (Mean) 28 449 450 -0.5 27 19 367 350 2.7 19 28 255 261 2.8 27 28 120 129 12 27 27 99 99 5.8 27 Placebo TR N Baselin e (Mean) Endpoin t (Mean) % Change (Mean) 44 710 750 7.2 48 29 537 571 18.7 33 44 272 271 0.4 48 44 272 28 5.0 48 42 100 90 -4.2 45	N Baselin e (Mean) Endpoin t (Mean) % Change (Mean) N (Mean) Baselin e (Mean) 28 449 450 -0.5 27 432 19 367 350 2.7 19 350 28 255 261 2.8 27 252 28 35 36 4 27 34 28 120 129 12 27 128 27 99 99 5.8 27 92 Placebo TRICOR N Baselin e (Mean) Change (Mean) e (Mean) 44 710 750 7.2 48 726 29 537 571 18.7 33 543 44 272 271 0.4 48 261 44 272 28 5.0 48 30 42 100 90 -4.2 45 103	N Baselin Endpoin Change (Mean) (Mea

* = p<0.05 vs. Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia².

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

Type I (rare) IIa IIb		Lipid Elevation				
Type	Lipoprotein Elevated	Major	Minor			
I (rare)	chylomicrons	TG	1-C			
IIa	LDL	С	-			
IIb	LDL, VLDL	C	TG			
III (rare)	IDL	C, TG	_			
IV	VLDL	ŤG	1÷C			
V (rare)	chylomicrons, VLDL	TG	1			

C=cholesterol
TG=triglycerides
LDL=low density lipoprotein
VLDL=very low density lipoprotein
IDL=intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle
Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [†] or CHD risk equivalents (10-years risk >20%)	<100	≥100	≥130 (100-129:drug optional) ^{††}
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk Factor ^{†††}	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD = coronary heart disease

Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 107 mg to 160 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 107 mg to 160 mg TRICOR per day and was 0% in those receiving dosages equivalent to 54 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of TRICOR and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tendemess, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 160 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take

TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter² of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter² surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter² surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter² surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter² surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60%

increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM	Fenofibrate*	Placebo
Adverse Event	(N=439)	(N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diamhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL D	DISORDERS	
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%

SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

Dosage equivalent to 200 mg TRICOR

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

ENDOCRINE SYSTEM: Diabetes mellitus

HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.

SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should

^{**.} Significantly different from Placebo

continue this diet during treatment with TRICOR. TRICOR tablets should be given with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 160 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 54 to 160 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 160 mg per day.

Treatment with TRICOR should be initiated at a dose of 54 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 54 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR™ (fenofibrate tablets) is available in two strengths:

54 mg yellow tablets, imprinted with ≡ and Abbo-Code identification letters "TA", available in bottles of 90 (NDC 0074-4009-90).

160 mg white tablets, imprinted with ≡ and Abbo-Code identification letters "TC", available in bottles of 90 (NDC 0074-4013-90).

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Laboratoires Fournier, S.A., 21300 Chenôve, France

Made in France

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Revised: NEW



TRICOR® 48 mg and 145 mg

(fenofibrate tablets)

$m R\!\!\!\!/$ only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 48 mg or 145 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:

The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains hypromellose 2910 (3cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate.

In addition, individual tablets contain:

48 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D&C Yellow #10 aluminum lake, FD&C Yellow #6 /sunset yellow FCF aluminum lake, FD&C Blue #2 /indigo carmine aluminum lake.

145 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained in vivo in transgenic mice and in vitro in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPAR α). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPAR α also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

Exposure to fenofibric acid in plasma, as measured by C_{max} and AUC, is not significantly different when a single 145 mg dose of fenofibrate is administered under fasting or nonfasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) with pravastatin (40 mg) once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3 α -hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively in 23 healthy adults.

A single dose of pravastatin had no clinically important effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) with atorvastatin (20 mg) once daily for 10 days resulted in approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 145 mg TRICOR (fenofibrate tablets) per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1
Mean Percent Change in Lipid Parameters at End of Treatment[†]

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid				
values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL		,		
and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid				
values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL				
and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid				
values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

[†] Duration of study treatment was 3 to 6 months.

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 145 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2
Effects of TRICOR in Patients With Fredrickson
Type IV/V Hyperlipidemia

TRICOR
e N Baseline Endpoint % Chan (Mean) (Mean) (Mean
27 432 223 -46.2*
19 350 178 -44.1*
27 252 227 -9.1*
27 34 40 19.6*
27 128 137 14.5
27 92 46 -44.7*
TRICOR
e N Baseline Endpoint % Chan (Mean) (Mean) (Mean
48 726 308 -54.5*
33 543 205 -50.6*
48 261 223 -13.8*
48 30 36 22.9*
45 103 131 45.0*
45 126 54 -49.4

^{*=} p < 0.05 vs. Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

^{*} p = < 0.05 vs. Placebo

INDICATIONS AND USAGE.

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of

TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia².

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

		Lipid H	Clevation	
Туре	Lipoprotein Elevated	Major.	Minor	
I (rare)	chylomicrons	TG	↑↔C	
Ìla	LDL	C	-	
IIb	LDL, VLDL	C	TG	
III (rare)	IDL	C, TG	•	
ÌV	VLDL	TG	1↔C 1↔C	
V (rare)	chylomicrons, VLDL	TG	1↔C	

C = cholesterol TG = triglycerides

LDL = low density lipoprotein

VLDL = very low density lipoprotein

IDL = intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD isk equivalents (10-years risk > 20%)	< 100	≥ 100	≥ 130 (100-129:drug optional)††
2+ Risk Factors 10-year risk ≤ 20%)	< 130	≥ 130	10-year risk 10%-20%: ≥ 130 10-year risk < 10%: ≥ 160
0-1 Risk Pactor†††	< 160	≥ 160	≥ 190 (160-189: LDL- lowering drug optional)

CHD = coronary heart disease

Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

the Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

After the LDL-C goal has, been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 96 mg to 145 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 96 mg to 145 mg TRICOR per day and was 0% in those receiving dosages equivalent to 48 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also CLINICAL PHARMACOLOGY, Drug-drug interactions).

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gall-

bladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 145 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR (fenofibrate tablets) with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD) of 145 mg/day, based on mg/meter² of surface area). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/meter² surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and Gemfibrozil (250 mg/kg/day; 2 times the human dose) (multiples based on mg/meter² surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the MRHD on the basis of mg/meter² surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at the same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/meter² surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of approximately 9 times the MRHD of 145mg/day of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 10 times the MRHD to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of approximately 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of fenofibrate at 9 to 18 times the MRHD to female rabbits caused abortions in 10% to 25% of dams and death in 7% of fetuses at 18 times the MRHD.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		•
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

Dosage equivalent to 145 mg TRICOR

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

^{**} Significantly different from Placebo

DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

ENDOCRINE SYSTEM: Diabetes mellitus.

HEMIC AND LYMPHATIC SYSTEM: Anemia. leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, allergic pulmonary alveolitis, pneumonia, laryngitis, and sinusitis.

SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, abnormal kidney function, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR tablets can be given without regard to meals.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 145 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 48 to 145 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 145 mg per day.

Treatment with TRICOR should be initiated at a dose of 48 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 48 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR® (fenofibrate tablets) is available in two strengths:

48 mg yellow tablets, imprinted with and Abbo-Code identification letters "FI", available in bottles of 90 (NDC 0074-6122-90).

145 mg white tablets, imprinted with and Abbo-Code identification letters "FO", available in bottles of 90 (NDC 0074-6123-90).

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Fournier Laboratories Ireland Limited, Anngrove, Carrigtwohill Co. Cork, Ireland

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ABBOTT



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RESCRIPTION

Antiara (tendibrate) Capsules, is a ligid regulating agent available as capsules for oral administration. Each capsule contains 43 mg, 87 mg, or 130 mg of nicronized tenditarate. The chemical name for fendibrate is 2-14-14-chlorobenuryli phenoxyl-2-methyl-propandic acid. 1-methylethyl ester with the following structural formula:

الأحد ال

The empirical formula is $C_{\infty}H_{\infty}Q_{\alpha}Cl$ and the molecular weight is 350.83; tenoforate is associable in water. The monthing point is 79° -52°C. Fenoforate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each gelatin capsule contains super spheres, hypromeliose, sodium hauryl subste, denethicone, simethicone, and talic. The gelatin capsules also contain suster dioxide, intenium dioxide, yekkwi inn oxide, indigo carmine FDEC Blue #2, DAC Yellow #10 and black infl. CLINICAL PHARMACOLOGY

CLINICAL PRARMADILION

A visity of chical studies have demonstrated that elevated levels of total choksterol (total-C), low density lipoprotein cholesterol

CDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human afterosaterosis. Similarly, decreased levels of
high density ipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo A) and apo A)) are associated with the development of afterosaterosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the
level of lotal-C, LDL-C, and trighteenides, and inversely with the level of HDL-C. The independent effect of reising
HDL-C on beying tatyporties (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fending calculate established (terroforate, produces reductions in total classisterol, LDL cholesterol, apolipoprotein B, total trighteening and the produces in the activity of the produces in the contribute static hearting to the contribute of the produces are bits desirated and the produces are better and the produces are bits desirated and the produces are better and the produces are bits desirated and the produces are better and the produc

ericises, and bilolyceride nich lipoprotein (M.DL) in treated pallents, in addition, treatment with terrofibrate meants in increases in high o

eries, and higheride rich lipoprotein (N.D.) in treated patients, in addition, treatment with terrotorate meads in increases in high density important (RDL) and approfession good and approfession good. In the first of terrotoric section of perceivance and incertain produce have been explained in vivo in transgenic mice and in vitro in human hispotocyte cultures by the activation of perceivance producers and eliminate producers and eliminate producers of explaining the production of appropriate C-111 (an inhibitor of disportation lipsase activity). The resulting lain highers less produces and reducing production of appropriate C-111 (an inhibitor of disportation lipsase activity). The resulting lain highers less produces an attention in the size and compression of LDL from small, dense particles (which are of thought to be attended to their susceptibility to oxidation), to large budyant particles. These larger particles have a greater affeitly for cholesterol recipiers and are calaboticed rapidly Autorition of PRAPs, size induces an invesse in the synthesis of appropriate AL A-11 and RDL cholesterol.

Fendinate above close source in contains in the synthesis of appropriate AL A-11 and RDL cholesterol.

Pharmacokinetics/Metabolism
Plasma concentrations of fenotivic acid after multiple cose administration of Antara 130 mg capsules are equivalent, under low-fat fed conditions, to 200 mg fenofibrate capsules.

Asserption
The aboution bioaveilability of tenoforate connot be determined as the compound is virtually insoluble in acusous media suitable for injection. However, fundificate is well absorbed from the postrointestinal tract. Following or all administration in healthy volunteers, approximately 50% of a single does of radioacticed fendificate appeared in urine, primarily as tenofitaric acid and is glucumonate conjugate, and 55% was contect in the focus Peak plasma levels of tenofibric acid from Antara occur within 4 to 8 hours after administration.

There was less than dose-proportional increase in the systemic exposure of tenofibric acid from three strengths (43 mg, 87 mg, and 130 mg) of Antara under fasting conditions.

Does of two- or three-capsades of 43 mg Antara given concurrently were dose-captratent to single-capsade doses of 87 mg and 130 mm presentitions.

130 mg, respectively.

The enterf of biosphion of acid was unaffected when Antara was taken eiter in tasted state or with a tow-fat meat. However, the C, Antara Increased in the presence of a low-fat meat. I _{max} was unaffected in the presence of a low-fat meat. In the presence of a hig meat, there was a 26% increase in AUC and 100% increase in C_{max} of fenditivic cod from Antara relative to tasting state.

Dichibatio

in resulting volunteers, steady-state plasma levels of tempforic acid were shown to be achieved within a week of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperinidems subjects.

Metaholism Following oral administration, tendilibrate is rapidly hydrotyzed by esterases to the active metabolite, fendilibric acid; no unchanged tendi-

Training test assessment, television or require injury reproduced by case acts to the active intercest, terriance and, no meanings security to the state of the case of the ca significant extent.

Excretion
After absorption, terrolibrate is mainly excreted in the urine in the form of metabolites, primarily benofibric acid suid tenofibric acid glucuronide.
After administration of radiolabelled tenofitrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the leces.
Fenofibrate acid from Antara is eliminated with a half-life of 23 hours, allowing once daily administration in a clinical setting.

Special Populations

behalms in electry volunteers 77–87 years of age, the oral clearance of tenofibric acid tolowing a single oral does of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the effectly, without increasing accumulation of the drug or metabolities.

Antara has not been investigated in adequate and well-controlled trials in pediatric patients.

No pharmacokinetic difference between males and temales has been observed for lexofibrate.

have. The influence of race on the pharmocokinetics of fenofibrate has not been studied; however, fenofibrate is not metabolized by enzymes known for exhibiting other-ethnic variability. Therefore, inter-ethnic pharmocokinetic differences are very unlikely. Renal insufficiency.

Renal insufficiency in success and the property of the second state of the second stat

Hepatic insufficiency
No pharmacokinatic studies have been conducted in patients having hepatic insufficiency. Drug-drug Interactions

In vitro studies using human liver microsomes indicate that tenditizate and tenditizic acid are not inhibitors of cytochrome (CYP) P450 is forms CYP3A4, CYP205, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A5, and mixt-to-moderate inhibitors of CYP2

at merapeane concurrances.

Potentation of counsain-type anticoopulants has been observed with protongation of the protonomin time-RNR.

Bits acid sequestrants have been shown to bind other drups given concurrently. Therefore, terrolibrate of out-of-between at least 1 hour before or 4-6 hours after a bits acid binding resin to avoid impeding its absorption (see WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familia) and Nontamilial) and Mixed Dyslipidemia

rickson Types Ita and (th)

The effects of tenofibrate at a cose equivalent to 130 mg Antara per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline tipd, values, total-C 305.9 mg/dt; DDL-C 213.8 mg/dt.; HDL-C S23 mg/dt, and brighycardice 191.0 mg/dt. Perofabrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Ferrofabrate therapy stop lowered trighycardice and mised HDL-C (see Table 1).

Mean Percent Change in Lipid Parameters at End of Treatment ¹					
Treatment Group	Total-C	LDL-C	HDL-C	TG	
Pocied Cohort Moon baseline fland values (n=645) All EEN (n=361) Placebo (n=285)	306.9 mo/d. -18.7% -0.4%	213.8 mg/dL -20.5% -2.2%	52.3 mg/d2 +11.055* +0.7%	191.0 mg/di. -28.9% +7.7%	
Buseline LDL-C > 160 mg/dL and TG <150 mg/dL (Type 11z) Mean baseline jand values (n=234) All FEN (n=193) Placebo (n=141)	307.7 mg/dL -22.4%* +0.2%	227.7 mg/dL -31.4%* -2.7%	58.1 mg/dl. +9.8%* +2.6%	101.7 mg/dl_ -23.5%* +11.7%	
Beseine LDL-C :>160 mg/dL and TG_150 mg/dL (Type 11b) Mean baseline (Ipid values on=242) All FEH (n=126) Pracebo (n=116)	312.8 mg/dL -16.6% -3.0%	219.5 mg/dL -20.1%* -5.5%	46.7 mg/dl +14.5% +2.3%	231.9 mg/dL -35.9%* +0.9%	

p=<0.05 vs. placabo

In a subset of the subjects, measurements of apo B were consusted. Ferolibrate treat ment eignificantly reduced apo B from baseline to ond-point as compared with placebo (-25,1% vs. 2.4%, p.<0.0001, n=213 and 143 respectively).

Antara[™]

(fenofibrate) Capsules

Hypertriglyceridemia (Fredrickson Type IV and V)

injecting contains presentation type in 2 mary. The effects of test circo-images, double-band, placeto-controlled clinical triefs of 147 hypertrighted clinical triefs of 147 hypertrighted clinical triefs of 147 hypertrighted patients of test indicated controlled clinical triefs of 147 hypertrighted patients with baseline highest 610 here of 500 to 1500 mg/d, and the other 150 here's of 350 to 500 mg/d, and the other 150 here's of 350 to 500 mg/d, and the other 150 here's of 350 to 500 mg/d, in patients with the partrighted contains a form of the clinical patients with 150 mg/d hypertrighted contains a final patient with the partrighted at double contains a form of the 150 mg/d hypertrighted contains the patients of patients with 170 mg/d hypertrighted patients with 170 mg/d hypertrighted contains and of patients with 170 mg/d hypertrighted contains and of patients with 170 mg/d hypertrighted contains and of the 150 mg/d hypertrighted contains and the 150 mg/d hypertrighted contains and 150 mg/d hypertrighted co Epopratein (LDL) cholesterol (see Table 2)

Table 2. Effects of Fenofibrate in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1		Pla	cebo			Fe	nofibrate	
Baseine TG levels	•				•	. •		
350 to 499 mg/st.		Baseline	Endpoint	% Dunge		Baseline	Endpoint	% Change
	N.	(Mean)	(Mean)	(Mcard	H	(MEan)	(Mean)	(Mean)
Trigiyoerides	28	449	450	-0.5	27	432	223	-46 2*
VLDL Triglycerides	19	357	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	160	2.8	27	252	227	-9.1°
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	/8	120	129	12	27	125	137	14.5
VLDL Cholesterol	27	39	39	5.8	27	92	46	-44,7*
Study 2		Plac	ebo			Fenafi	brate	
Bassine TG levets								
500 to 1500 mg/dl.		Daseline	Enthoint	% Change		Baseline	Endpoint	% Change
	N	(Mean)	(Mean)	(Meare	21	(Mean)	(Mcan)	(Mean)
Triglycerides	14	710	750	7.2	48	726	308	-54.5 *
VLDL Triglyceristes	23	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	:71	9.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	125	54	-49.4*

⁼p<0.05 vs. piacebo

The effect of tenolibrate on cardiovascular morbisity and mortality has not been determined.

INDICATIONS AND USAGE Treatment of Hypercholesterolen

Antara is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerifos, and Apo B, and to Increase HDL-C in adult potients with primary hyperchoscientenia or mixed dystpidems friends with primary hyperchoscientenia or mixed dystpidems friends with 13 and 11b). Lipid-electing egents should be used in addition to a diet restricted in shartset of at and cholestered when response to del and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program (NCEP) Treatment Guidelines, below).

addition to a det restricted in saturated fat and christered when response to det and non-pharmacological interventions alone has been inadequate (see National Christered Education Program (NCCP) instrumed underliess, between Antara is take indicated as adjustance therapy to diet is a treatment of adult patients with hypertriphycoridemia Gredrickvan Types IV and V hypertriphycoridemia. Improving glycomic control in disbetic patients drawing lasting chylomiconamia will usually reduce fasting triphycerides and eliminate chylomiconomia thereby carviding the need for platimacologic intervention.

Markedy devaled levels of unam bylogication (pp. 2,000 mg/dl. may increases the risk of developing paracreatiss. The effect of Antara therapy on reducing this risk has not been adequately studed.

Drug therapy is not indicated for patients with Type I bypertipoprotetinemia, who have elevations of chylomicrons and plasma trighycerides, but who have normal levels of very low density tipoprotetinemia, who have elevations of chylomicrons and plasma trighycerides, but who have normal levels of very low density tipoprotetinemia.

The initial teatment for dystipational is delary therapy specific for the type of tipoprotein abnormality. Excess body weight and excess also-holic intotax may be important factors in hypertriphyceridemia and chould be addressed prior to any drug therapy. Physical exercise can be an important ambary measure. Dissesses one blady to hypertripheria, such as hypothyroidem or diabetes refused suitable to looked for and adequately treated, Edinogen therapy. But histante districts and beta-blockers, is sometimes associated with measure rises in plasma riplycerides, specially in substants though the part expenditions. It the decision is made to use drugs, the patient should be instructed that this does not reduce the Importance of adhering to detice the Walkinko's and PRECAUTIONS.

Fredrickson Classification of Hyportipoproteinemias

	Fredrick	son Classification of Hypertipopro	deinemias	
_			Lipid Eleration	
Тур	E Lipoprotein	Elevated Major	f	Minor
I ya	re) Chylomi	crons TG		1 +C
114	1.00	C		-
111	I DL, V	LDI C		7G
131 pr	are) IDI	. C, 10	i	-
10	. ND	L TG		1 ↔C
V fra	rei Chylomicro	ns, VLDL TG		1 44

C-chriesteni

TG=triglycerices LDL=low density lipoprote

VLDL=very low density lipoprotein ity beauter

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goaf (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Lovel at Which to Consider Drug Therapy (mg/dL)
CHD [†] (a CHD risk equivalents (10-year risk >20%)	<100	»160	≥130 (100-129: drug optionat) ^{‡‡}
2+ Risk Fectors (10-year risk ≤20%)	÷130	≥130	10-year risk 10-20%: ≥130 10-year rick <10%: ≥160
0-1 Rick Factor III	160	≥160	≥190 (160-159: LDL-lowering drug optional)

CHD-coronary heart disvase.

Some sufficiency for a LDL-bavering drugs in this category if an LDL-C level of <100 mg/dL cennot be achieved by the repeallo litestyle changes. Others prefer use of crugs that primarily modify brighterides and HDL-C, e.g., nicotinic acid or fibrate. Clinical palgement also may cell for deferring drug therapy in this subcategory.

Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not

After the LDL-C goal has been achieved, if the TG is still >200 mg/dl., non-HDL-C (total-C minus HDL-C) becomes secondary target of thorapy, Kon-HDL-C goals are set 3.0 mg/dl. higher tran LDL-C goals for each risk category.

CONTRAINDICATIONS

CONTINUATIONS.
Anisa's commandicated in patients who entitle hypersensitivity to fenotibreix.
Fenotiable is contracticated in patients with hepatic or severe meal dystunction, britising primary billway contoxis, and patients with merplained persistent liver function abnormality.
Fenotibratio is contracticated in patients with preensiting gallolacter disease (see WARMINGS).

WARMONS

Liver Functions fencionate at doors equivalent to 67 mg to 130 mg Antara per day has been associated with increases in servin transam-nases [AST (SGUT) or ALT (SGUT)). In a pointed analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 3.3% of patients being tendificate versus 1.1% of patients treated with placebo.

When transaminase determinations were (sinchware other after discontinuation on the relimination of uning continued treatment, a return to nor-mal limits was usually observed. The incidence of increases in transaminases related to tendificate therety appear to be dose related. In an exvest koose-raping study, the emidence of ALT or AST elevations to of lead first eithers the upper limit of normal stiffs, in patients receiving dosegues equivalent to 87 mg to 130 mg Antara per day and was 0% in those receiving dosegues equivalent to 43 mg or less Antara per day, or placebo, liquation-likidic chronic active and checistic hepotitis associated with threathorate therapy have been reported after expo-sures of weeks to surveral years. In extremely mark cases, christis has been reported in association with chronic active hepatids. Regular period; mornitoring of here hanclivin, industing serum ALT (SGPT) should be performed for the duration of therapy with Antara, and through discontinual of in-nyme beens period above three times the numeral limb.

Choledithiasis: Fendinata illo Undirate and genilibrati, may immass cholesteric exception into the bile, leading to choleithiasis. If

cholellhiasis is suspected, quiliblation utudies are mulcated. Antara therapy chauti be discontinued if gallstones are

ø

(fenofibrate) Capsules

Concomitant Oral Anticoagulants: Capture should be exercised when anticoagular is are given in conjunction with Antara because of this potentiation of counsaria-type anticoagularians in protonging the probromatin the aNRI. The design of the anticoagularian should be reclined to maritain the protonomin time-NRI at the design level to proven the learning complications. Frequent probromatin time-NRI at the design of the protonomin ment of the protonomin time-NRI has stabilized. Concomitant NRI-CoA reductase inhibitors: The combined use of Antara and NRI-CoA reductase inhibitors should be avoided unless the benefit of their attentions in high levels is likely to outwelf the increased into did this drop contribution. In a single-dose drug interestion titisty in 23 healthy adults the concomitant administration of functionate and provastation in a single-dose drug given alone.

In a single-dose drug given alone.

The combined use of Invite acid demonstrates and HAG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with histotomyotysis, markedly elevated or estime k-mass (OG levels and myoglotin-urfu, leading in a high proportion of cases to scrute read fabrae.

The combined use of Invite acid demonstrates and HAG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with histotomyotysis, markedly elevated or estime k-mass (OG levels and myoglotin-urfu, leading in a high proportion of cases to scrute read fabrae.

The use of fibrates alone, including Antara may occasionably be associated with myositia, myopathy, or inabdomyotysis, Patents receiving Antara and complaining of muscle pain, including and marked pharmacological and complaining of muscle pain, including service in facilities level determination. It myopathylympocials is suspected or dispneed, Antara mary should be stopped.

Mortality: The effect of Antara on coronary hard disease morbi

PRECAUTIONS

PRISEAUTURES
initial Therapy: Laboratory studies should be done to excertain that the lipid levels are consistently abnormal before Instituting Antora therapy. Every effectly should be made to control serum lipids with appropriate dist, exercise, weight lass in libbare patients, and control or any medical proxidems auch as oldated a meltius and hypothyridism that are contributing to the lipid abnormals. Medications known to exacertate hypertriphycardemia (beta-blockers, thiazides, estrogenst should be discontinued or changed if possible prior to consider-

to exceptable hypertrighyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or unanged in possible pror to consideration of highestide-lowering drug therapy.

Continued Therapy Portical determination of earum lipids should be obtained during initial therapy in order to establish the lowest effective does of Artara. Thirapy should be withdrawn in patients who do not have an eduquate response after two months of treatment with the maximum recommented free of 130 mper day.

Pascreatitiss Pancreatitis has been reported in patients taking tenderate, genfilms all, and clotiforate. This concerned may represent a return of efficiency in patients with severe hypertrighyceridemia, a direct drug effect, or a secondary phenomenon mediated through believ tract stone or skidge formation with obstruction of the common bile duct.

Hypertrightity Reactions. Ands hypertrightity reactions including server skin rishes requiring patient hospitalization and treatment with strotics have occurred very rarely during treatment with tenoforate, including care spontaneous reports of Stevers-Johnson synctrone, and turce dependent incomplysis. Unicaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of ferrofibrate and placebo preferes, respectively, in controlled trials.

italogic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in potients fullow

remainings changes will be most in the control to t phokinase (CPIO levels.

Patients should be advised to report promptly unexplained muscle pain, tendemess or weakness, particularly if accompanied by makins or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions:

by elevated OPK levels occur or impropath is diagnosed.

Drug Interactions:

Oral Anticoagustants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ANTICOAGULANTS CAUTION.

ANTARA. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTINGOMEN THAMPIN AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPULATIONS. PREQUENT PROTINGOMEN THAMPIN DETERMINATIONS ARE ADVISABLE UNTIL IT MAS BEEN DEFINITION. THE PROTINGOMEN THAMPIN AS STABLIZED.

HING-COA Reductase inhibitors: The combined rus of Antica and HING-COA Reductase inhibitors: The combined rus of Antica and HING-COA Reductase inhibitors: The combined rus of Antica and HING-COA Reductase inhibitors: The combined rus of Antica and HING-COA Reductase inhibitors: The combined rus of HING-COA Reductase inhibitors: The combined rus of Antica and HING-COA Reductase inhibitors: The combined rus of HING-COA REDUCTION RUS of Antica Reductase Inhibitors: The Antica Reductation Reductase Reductase Inhibitors: The Antica Reductase Inhibitors: The Antica Reductase Reductase Inhibitors: The Antica Reductase Inhibitors: The Reductase Reductase Inhibitors: The Reductase

brath: hepatic neoplastic nodules were horecased in makes and ternakes threated with gemilibraril while testicular introstitial cell tumors were increased in makes on all threat drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 17 and 3 times the maximum recommended human dose on the basic of implicated guidace break), there were statisticatly significant increases in liver carcinoma at 3 times the maximum recommended human dose in both makes and temples. In a second 16-month study at this same doses, there was a significant increase in liver carcinoma in make mice and the receivance in termals mice at 3 times the maximum recommended human dose. Pectorn microcopy studies have demonstrated perodoxomal prodiferation following fenchistrate administration to the rat As adequate study to test for peroxisome proliferation in humans have been done, but changes in peroxisome proliferation in humans have been done, but changes in peroxisome proliferation in those some difference and after the first class when I ver biopsics were compared before and after the terrification to have been designed.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal

Fendibrate has been demonstrated to be devoid of mutagenic potential in the following tester Ames, mouse symptomic, crowning aberration, and unscheduled DNA symbols.

Pregnancy Editspory C. Fendibrate has been shown to be embryocidal end terefogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose on the basis of ingrinder? surface area. There are no acceptate and well-controlled studies in pregnant women. Fendibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the felus.

Administration of 9 times the maximum recommended human dose of fendibrate to temple rate buffer and troughout gestation caused 100% of dams to deby delivery and resulted in a 60% increase in post-implantation loss, a decrease in filter size, a decrease in bith weight, a 40% survival of pups at birth, a 4% survival of pups as necroites, are a 6% survival of pups to wearing, and an increase in spina britida.

In spinal bifide.

Administration of 10 times the maximum recommended human doze to furnate rate on days 6-15 of gestarion ocused an increase in gross, viscoral and skeletal findings in febuses (comed head/hundhed shoulders/rounded body/abhormal chest, kyphosis, shufted febuses, extrapted sternal ribs, mationned demokrae, extra foramen in polatine, misstagen vertebrae, cupernumerary ribes. Administration of 7 Unes the maximum recommended human dose to female rate bind may 15 of gestation through searing caused a delay in delivery, a 40% decrease in like births, a 75% decrease in neonatal survival, and decreases in pur weight, at birth as well as on days 4 and 22 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused obortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and d-valt of 7% of fetuses at 18 times the maximum recommended human dose and d-valt of 7% of fetuses at 18 times the maximum recommended human dose and d-valt of 7% of fetuses at 18 times the maximum recommended human dose.

onnered trainen dose.

Norsing mothers: Fersibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue rursing or to discontinue the grug.

Pediatric User Solety and efficacy in pediatric potients have not been established.

Antara[™] (fenofibrate) Capsules

Geriatric Use: Fenotitric acid is known to be substant ally excreted by the kidney, and the risk of acverse reactions to this drug may be greater in patients with impanted renal function. Gozanae elderly patients are more lifely to have decreased renal function, care should

ADVENSE REACTIONS
CLINICAL: Adverse events reported by 2% or more of patients treated with fundificate during the double-blind, place? o-controlled trials, regardless of causality, are lasted in the table below. Anverse events ted to discominuation of treatment in 5.1% of potients treated with fenditorate and in 3.0% treated with placebo. Increases in liver function tusts were the most frequent events, causing discontinuation of tendibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Ptacebo (N=366)	
BODY AS A WHOLE			
Abdominal Pain	4.6%	4.4%	
Back Pain	3.4%	2.5%	
Headache	3 2%	2.7%	
Asthenia	2.1%	3.0%	
Fiu Syndrome	2.1%	2.7%	
DIGESTIVE	•		
Liver Function Tests Abnormal	1.5%**	1.4%	
Distriba	2.3%	4,1%	
fiausea	2.3%	1.9%	
Constinution	4.1%	1.4%	
METABOLIC AND			
NUTRITIONAL DISCRIDERS			
SGPT increased	3 0%	1.5%	
Creatine Phospholdnase Increased	3.0%	1.4%	
SGOT Increased	1,4% **	0.5%	
RESPIRATORY			
Respiratory Disorder	6.2%	5.5%	
Rhinitis	2.3%	1.1%	

Dosage equivalent to 130 mg Antara

Sprillantly different from planeto
Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials,
regulates of counselts are birted before.

800Y AS A WHOLE: Chest pain, pain (unspecified), infection, mainise, allerge, reaction, cyst, ternia, lever, photosens-tivity reaction, and

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasuolitatation, coronary artery disorder, electrocardiogram abnormal, ventricu-

CARDINASCELAR SYSTEM Anging pectors, hypertenson vasodistation, coronary artary disorder, electrocardiogram abnormal, varificular entraspositios, impocardia influent, peripheral vasocial disorder, migrater, varicos even, cardiovascular disorder, propheral vasocial disorder, migrater, varicos even, cardiovascular disorder, amprimina, pribebilis, lachycurda, extrasystoter, and obtai librillation.

DIGESTIME SYSTEM Physiopes, flatalience, missea, increased reporter, describententis, cheelibilisais, rectal disorder, escapagita, operitis, cold, forth disorder, vaniting, amereis, gastremiseriand disorder, duvidental sileor, neutrea and vomiting, peptic ulcer, rectal hemorrhage, lives latty deposit, cholecystitis, eructation, gamma plutomyl transpertidase, and disorbea.

EMOCRINE SYSTEM Disbettes mellitus.

EMDICATION: 5 TO ILAN DIADETED TREUMIN.
HEMECAND UNPAYANTIC STSTEM Anemia, Isukaperia, eachymosis, cashophilia, lymphademopathy, and thrombocytopenia.
METABOUC AND NUTRITIONAL. DISORDERS: Circatinine increased, weight gain, hypogycemb, godt, weight bass, edema, hyperuncemia, and

pergineral cuerra. MUSCIA.OSKELETAL SYSTEM Myositis, niyalqia, arthrakçia, arthraki, tenosynovitis, joint disorder, arthrosis, leg cromps, bursitis, and

mvasthenia. MERVOUS SYSTEM: Dizziness. Insurmita, depression, vertiga, libido docreased, andiety, parestresak, dry mouth, hypertoola, norvou .

raţia, and somnotance.

RESPRATION STSTEM: Pharyngitis, brunchiis, cough norwazed, dysprea, asthma; preumonia, bryngitia, and sinusitis.

RESPRATION STSTEM: Pharyngitis, brunchiis, cough norwazed, dysprea, asthma; preumonia, bryngitia, and sinusitis.

SRM AND APPENDAGES Read, pruffus, scizena, herper miche, uritraija, one, sweating, langid dermatilis, skin cisorder, aloperia, contact dermatilis, herpes simplex, manulopapular trash, rail disorder, and clin utcer.

SPECIAL SENSE Conjunctivis, eye disorder, armbyogu, eze pain, orbits media, abrommal vision, catarect specified, and refraction disorder.

URDECHILLA STSTEM: bitrary frequency prostatic onorder. dyouria, kidney function abnormal, urolithicsis. Synecomastia, unintended pregnancy, vaginal monitasis, and cystits

OVERDOSAGE

There is no specific treatment for overdose with Antara. General supportive care of the patient is indicated, including monitoring of vital signs and observation of direct status, should an overdose occur. It indicated, elimination of unabsorbed drug should be achieved by enesits or gastic terage; usual precalutions about the observed to matritain the airway. Because fenolitarate is highly bound to plasma proteins, hemodialysis about not be considered.

DOSAGE AND ADMINISTRATION

Patents should be places on an appropriate lipid-lowering diet before receiving Antara, and should continue this diet during treatment with Antara. Antara capsules should be taken with mexis, thereby optimizing the bloovaliability of the medication.

For the treatment of adult patients with primary trepercholesterolemia or mixed hypertipidenta, the wittlet dose of Antara is 130 mg

For adult patients with hypertrephrendema, the initial doze is 43 to 130 mg per day. Dosege should be individualized according to patient response, and should be adjusted if necessary following repeat haid determinations at 4 to 8 week intervals. The maximum dose

an response, and whom we adjusted in the second of the sec efter evaluation of the effects on romal function and spid levels at this dues. In the effect, the initial does should likewise be finited to 43 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of Antara if lipid levels tell sig-

afficiently below the targeted range

HOW SUPPLIED

Antara (fenofibrate) Capsules, is available in three strengths:

43 mg capsules, imprinted with "43" and a segmented band, on the light green cap and "ANTARA" with the Refiert logs on the white to off-white body, available in buttles of 30 (RDC = 65776-401-10) and 10) (NDC = 65726-401-25).

87 mg causules, imprinted with 187° and a segmented band, on the dark groun cap and "ANTARA" with the Refard logo on the light green body, available in bottles of 30 (NDC • 65726-402-11) and 100 (NDC • 65726-402-25).

130 mg capsules, Imprinted with "130" and a premented band, on the dark green cap and "ANTARA" with the Relant logo on the white body, available in bottles of 30 (NDC # 65725-403-1) in and 100 (NOC # 65726-403-25).

Store at 25°C (77°F); excursions permitted to 15° -30°C (59°- 86°F); [see USP Controlled Room Temperature] in a tightly closed container.

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